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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/211,297	12/14/98	BOYLE	W A-451-F

EXAMINER

021069
AMGEN INCORPORATED
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS CA 91320-1799

HM12/0312

ART UNIT	PAPER NUMBER
1647	9

DEFERRY,R

DATE MAILED: 03/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/211,297	BOYLE, WILLIAM J.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Status of Application, Amendments and/or Claims

The information disclosure statement filed 27 December 2000 (Paper No. 7) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits. Claims 1-36 have been cancelled (Paper No. 3, 25 March 1999). Claims 37-47 were added, however Applicant inadvertently omitted claim 43 (Paper No. 3, 25 March 1999). Examiner has made corrections under rule 126. Claims 37-47 have been renumbered as 37-46. Claim dependencies have been corrected under rule 126. The amendment filed 27 December 2000 (Paper No. 8) has been entered in full. New claims 48-58 (Paper No. 8) have been renumbered as 47-57. Claims 37-57 are now under examination.

Withdrawn Objections And/Or Rejections

The objection to claim 41 as set forth at page 2 of the previous office action (Paper No. 5, 27 March 1999) is *withdrawn* in view of the amended claim (Paper No. 8, 27 December 2000). The rejections of claims of claims 37-46 under 35 USC 112, first paragraph as set forth at pages 2-3 of the previous office action (Paper No. 5, 27 March 1999) are *withdrawn in part in* view of the amended claims (Paper No. 8, 27 December 2000). Please see section on 35 USC 112, first paragraph, written description. The rejections of claims 37-46 under 35 USC 112, second paragraph as set forth at pages 3-4 of the previous office action (Paper No. 5, 27 March 1999) are *withdrawn* in view of the amended claims (Paper No. 8, 27 December 2000).

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. If the filed drawings are formal drawings, please indicate as such in response to this Office action and the drawings will be reviewed by the draftsman.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 37 is drawn to a composition comprising an antibody or fragment thereof which binds to an osteoprotegerin binding protein and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant, wherein the antibody or fragment is present in an amount effective to inhibit bone resorption in a patient, and wherein the osteoprotegerin binding protein comprises the amino acid sequence of Figure 2 (SEQ ID NO: 37), Figure 4 (SEQ ID NO: 39), a naturally occurring variant thereof, a soluble form thereof, or a fragment thereof. The specification fails to teach how to administer the antibody or fragment thereof or the effective amount necessary to achieve inhibition of bone resorption in a patient. In

addition, claim 37 cites " a composition comprising an antibody or fragment thereof which **binds** to an osteoprotegerin binding protein" instead of **specifically binds** to an osteoprotegerin binding protein. An antibody or fragment thereof which binds nonspecifically would not be expected to inhibit bone resorption.

Lastly the specification does not teach how to make antibodies against all naturally occurring variants, soluble form thereof, or fragments thereof of SEQ ID NO: 37 or SEQ ID NO: 38 or how to test specific antibody binding to all naturally occurring variants, soluble form thereof or fragments thereof of SEQ ID NO: 37 or SEQ ID NO: 38. On page 47 of the specification, only recombinant murine OPG binding protein (158-316) has been used as an antigen for immunization of animal. In addition, Applicant has not shown where the antibody specifically recognizes this partial sequence of murine OPG binding protein (158-316) such as in a western or immunoprecipitation assay. An antibody or fragment thereof which binds to an osteoprotegerin binding protein will be made against the determinants or the epitopes of the binding protein. There can be linear or conformational determinants. Epitopes formed by adjacent amino acid residues in the sequence are linear determinants. In contrast, conformational determinants are formed by amino acid residues from separated portions of the linear amino acid sequence that are spatially juxtaposed only upon folding. There are also neoantigenic determinants that result from modifications such as phosphorylation. Protein folding, denaturation, and certain modifications will all affect the specificity of binding of an antibody to an epitope (see Abbas *et al.*). The specification provides no guidance on how make antibodies against all naturally

occurring variants thereof, soluble form thereof or fragment thereof of the claimed protein and how to test specific antibody binding to all naturally occurring variants, soluble form thereof or fragment thereof of the claimed protein. In addition, a fragment thereof of osteoprotegerin binding protein reads on one amino acid, the size of a linear determinant that forms specific contact with an antibody is at least six amino acids.

Furthermore, claim 48 is drawn to a composition comprising an antibody or fragment thereof and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant, wherein the antibody or fragment is present in an effective to inhibit bone resorption in a patient, and wherein the antibody is produced by immunization with an osteoprotegerin binding protein comprising the amino acid sequence of Figure 1 (SEQ ID NO:37), Figure 4 (SEQ ID NO:39), a naturally occurring variant thereof, a soluble form thereof, or a fragment thereof. The claim does not state that this composition binds to an osteoprotegerin binding protein like claim 37. However, it's inherent that the antibody or fragment thereof would still be expected to binding specifically to an osteoprotegerin binding protein to inhibit bone resorption.

Applicant's arguments (pages 4-5, Paper No. 8, 27 December 2000) have been fully considered but are not deemed to be persuasive. Claims 37-45 as recited in the previous office action (Paper No. 5, 27 March 1999) embrace any antibody which will bind to any protein capable of binding to osteoprotegerin. Applicant argues that the claimed invention (a composition comprising an antibody or fragment thereof which binds to an osteoprotegerin binding protein and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant, wherein the antibody is

present in an amount effective to inhibit bone resorption) is described in terms of both structural and functional properties, and not simply by functional properties alone. This is not found persuasive because while Applicant has described full length and specific fragments of murine and human osteoprotegerin binding protein, Applicant has failed to describe any and all osteoprotegerin binding protein and hence the genus of antibodies specific for such proteins.

Due to the large quantity of experimentation necessary to make all variants and fragments of osteoprotegerin binding protein and to test specific antibody binding to all variants of osteoprotegerin binding protein, the lack of direction/guidance presented in the specification regarding the effective amount necessary to achieve inhibition of bone resorption in a patient, the absence of working examples directed to administering an effective amount to inhibit bone resorption in a patient, the complex nature of the invention, the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 37-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While the claims have been amended to describe the structural and functional properties of osteoprotegerin binding protein as SEQ ID NO:37 and SEQ ID NO:39 (Paper No. 8, 27 December

2000), the specification does not provide adequate written description for a composition comprising an antibody or fragment thereof which binds to an osteoprotegerin binding protein wherein the osteoprotegerin binding protein comprises naturally occurring variant, soluble form thereof and fragments thereof of the amino acid sequence of Figure 2 (SEQ ID NO: 37) or Figure 4 (SEQ ID NO: 39).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of antibodies directed against the full length sequences of osteoprotegerin binding protein (SEQ ID NO: 37 and SEQ ID NO: 39), the skilled artisan cannot envision every detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a composition comprising an antibody or fragment thereof which binds to an osteoprotegerin binding protein wherein the osteoprotegerin binding protein comprises the amino acid sequence of Figure 2 (SEQ ID NO: 37), Figure 4 (SEQ ID NO: 39), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 53 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 53 is drawn to the composition of claim 49 wherein the antibody or fragment is produced by recombinant DNA expression. Claim 53 is indefinite because, the claim does not set forth any steps involved in the method/process of recombinant DNA expression, it is unclear what method/process applicant is intending to encompass.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-2742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

RMD
March 7, 2001

ELIZABETH KEMMERER
PRIMARY EXAMINER